

## **REMARKS**

Claims 1-85 are pending in this application. Claims 1-19, 23-25, 29-32, 37-52, 55-57, 63-68, 70, 71 are cancelled. Applicants reserve the right to pursue the subject matter of any cancelled claims in this or a continuing or divisional application. No new matter is introduced. Claim 34 is amended to correct a typographical error that is supported by the remainder of the claims as originally filed. Claims 20-23, 26-28, 33, 35, 36, 53, 54, 58-62, 69, 72 are amended and are supported by the claims as originally filed and the specification at pages 5, and 55-56. New claims 73-85 are supported by the claims as originally filed.

***The objections to the specification and to claim 34 should be withdrawn.***

As stated above, applicants have submitted a sequence listing and amended claim 34. No new matter is introduced. Accordingly, the objections are rendered moot and applicants respectfully request withdrawal of the same.

***The rejections alleging indefiniteness under 35 USC § 112 should be withdrawn.***

The Office has rejected claims 23, 26-34, 39, 40, 55, 60, 61, 67-69, and 72 as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter as required under 35 USC § 112. Applicants respectfully disagree. Nonetheless, in an effort to advance prosecution and without acquiescing to the rejection, applicants have amended claims 23, 26-34, 39, 40, 55, 60, 61, 67-69, and 72 to recite that the underlying (*i.e.*, not mutated) TRAIL cytokine has the amino acid sequence of SEQ ID NO: 1. Accordingly, the rejections are now moot and applicants respectfully request their withdrawal.

The Office has also rejected claims 65, 66, and 71 under 35 USC § 112 for the alleged reasons set forth in pages 5-6 of the Office Action. Without acquiescing to the rejections, applicants have canceled claims 65, 66, and 71 but reserve the right to pursue the subject matter of these claims in this or a continuing application. The rejections are now moot and applicants respectfully request their withdrawal.

***The rejections under 35 USC § 101 should be withdrawn.***

The Office has also rejected claims 65 and 66 under 35 USC § 101 for the reasons set forth in page 6 of the Office Action. Without acquiescing to the rejections, applicants have canceled claims 65 and 66 but reserve the right to pursue the subject matter of the original claims in this or a continuing application.

***The rejections under 35 USC § 112, first paragraph should be withdrawn.***

Claims 35-38 and 70 are rejected under 35 USC § 112, first paragraph for allegedly failing to comply with the written description requirement. Applicants disagree.

According to the USPTO's guidelines for determining adequacy of written description, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species. *See* MPEP § 2163. The guidelines further note that “[w]hat constitutes a ‘representative number’ is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a ‘representative number’ depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed.” *Id.* Applicants submit that such a representative number species of the claimed genera are disclosed in the instant specification and claims as originally filed.

Nevertheless, without acquiescing to the rejection and in an effort to advance prosecution, applicants are amending claims 35-38 and 70 to recite “TRAIL cytokines having an amino acid sequence of SEQ ID NO:1” with mutations “at one or more amino acid positions of 130, 131, 149, 160, 195, 214, 218, and 220 to an amino acid residue other than alanine.” Accordingly, applicants believe the rejections are now rendered moot and respectively request their withdrawal.

Furthermore, applicants note that ages 39-43 of the as-filed specification provide experimental details about the production of both DR4- and DR5- selective TRAIL mutants. In addition, pages 42-48 describe functional analysis of these mutants and illustrate the receptor selectivity achieved by the specified mutations. Figures 7 and 8 of the as-filed specification show the specificity of TRAIL mutants for DR5 and DR4, respectively, as

determined using surface plasmon resonance; data for a large number (13, in fact) of the different TRAIL mutants falling within the scope of claim 20, among other claims, is shown.

In addition, applicants are submitting the declaration of Dr. Wilhelmus J. Quax with appended data and publications that demonstrate that the as-filed specification discloses processes for developing mutants falling within the scope of the presently claimed subject matter, and that one skilled in the art is able to obtain such mutants by following such processes.

In light of the present amendments, the as-filed specification, and the evidence submitted herewith in the declaration of Dr. Wilhelmus J. Quax, applicants submit that they have demonstrated possession of a representative number species such that one skilled in the art would understand that the inventors had possession of the claimed subject matter at the time the application was filed. Accordingly, applicants respectfully request withdrawal of the rejections under 35 USC § 112, first paragraph.

***The rejections under 35 USC § 102 should be withdrawn.***

The Office has rejected claims 20-28, 33, 54, 55, 57-60, 63-69, 71, and 72 under 35 U.S.C. 102(e) as allegedly anticipated by WO 20041001009 (the “Hymowitz publication”), filed June 23, 2003, which claims priority to US Provisional Application 60/391,050 filed June 24, 2002. Applicants disagree.

A proper rejection under 35 U.S.C. § 102 requires a showing that each limitation of a claim is found in a single reference, practice or device. *See In re Donohue*, 766 F.2d 531 (Fed. Cir. 1985). As shown below, the Hymowitz publication does not teach each and every element of the claims and thus does not anticipate the presently amended claims.

As a preliminary matter, without acquiescing to the rejection and in an effort to advance prosecution, applicants are amending claims 20-28, 33, 54, 55, 57-60, 63-69, 71, and 72 to recite, or depend from a claim that recites, one or more “TRAIL” cytokines “having an amino acid sequence of SEQ ID NO:1” with mutations “at one or more amino acid positions of 130, 131, 149, 160, 195, 214, 218, and 220 to an amino acid residue other than alanine.” Applicants note that none of these mutations is currently recited in the Hymowitz publication.

Thus, the Hymowitz publication does not teach each and every element of the claims and thus does not anticipate the claims as currently amended by the applicants. Accordingly, applicants respectfully request withdrawal of the rejection.

The Office has rejected claim 20-27, 54, 55, 57-59, 67, and 68 under 35 U.S.C. 102(b) as allegedly anticipated by WO 01100832 (the “Ashkenazi publication”) which was published January 4, 2001. Applicants disagree.

As applicants note above, the claims are currently amended to recite, or depend from a claim that recites, one or more “TRAIL” cytokines “having an amino acid sequence of SEQ ID NO:1” with mutations “at one or more amino acid positions of 130, 131, 149, 160, 195, 214, 218, and 220 to an amino acid residue other than alanine.” The Ashkenazi publication recites only one particular mutant for each of these positions, specifically alanine substitutions by the alanine scanning method. Thus, the Ashkenazi publication does not teach each and every element of the claims and thus does not anticipate the claims as currently amended by the applicants. Accordingly, applicants respectfully request withdrawal of the rejection.

***The rejections under 35 USC § 103(a) should be withdrawn.***

The Office has rejected claims 53 and 62 under 35 U.S.C. 103(a) as allegedly obvious in light of, and thus unpatentable over, US 2004 0146968 (the “Chung publication”), filed January 10, 2001. Applicants disagree.

While the Supreme Court has recently rejected a rigid application of the “teaching, suggestion, or motivation” as a factor in the obviousness analysis, the Court did reaffirm the Graham factors for the determination of obviousness. See *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727,1739 (2007). These four factual inquiries under Graham are: 1) determining the scope and contents of the prior art; 2) ascertaining the differences between the prior art and the claims in issue; 3) resolving the level of ordinary skill in the prior art; and 4) evaluating evidence of secondary consideration. *Graham v. John Deere*, 383 U.S. 17-18 (1966).

In determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. See *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*,

713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983); see also MPEP § 2141.02. Here, applicants claimed subject matter, as a whole, could not be obvious in light of teachings of the Chung publication.

As applicants note above, the claims 53 and 62 are currently amended to recite, or depend from a claim that recites, one or more “TRAIL” cytokines “having an amino acid sequence of SEQ ID NO:1” with mutations “at one or more amino acid positions of 130, 131, 149, 160, 195, 214, 218, and 220.” Here, the Office states that the Chung publication, together with general knowledge of one skilled in the art, suggests the methods recited in claims 53 and 62. The Office states, among other things, that the Chung publication “teaches that mutants with changed receptor binding affinity [for their] receptor are easily constructed by using the major amino acids of the receptor binding site” which is allegedly supported by Chung’s disclosure of a TRAIL “deletion mutant for residues 131-135” and the accompanying finding “that [the deletion mutant] had drastically reduced binding affinity and biological activity.” The Office concludes that this teaching “illustrates the obviousness of avoiding alteration of amino acids that interact with conserved receptor residues.” (Office Action, page 12).

First, if the deletion mutation disclosed by the Chung publication is relevant to the point mutations disclosed by applicants, it is an ambiguous teaching as one skilled in the art does not know which residue is responsible for the reduced binding. Furthermore, applicants have disclosed, among other things, that mutations at 131 do exhibit *increased* binding and/or selectivity/specificity for a target receptor, whereas the Office’s alleged teachings of the Chung publication demonstrate only reduced binding and biological activity.

Thus, the Chung publication teaches away from applicants teaching of the function of residue 131 of the TRAIL protein. “A reference may be said to teach away when a person of ordinary skill, upon reading reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.” *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). Furthermore, at a minimum, however, the Chung publication contains no teaching as to methods for increasing selectivity/specificity or binding of Apo2L/TRAIL to a target receptor.

Accordingly, in light of the Chung publication as a whole, the Office has failed to establish that the claimed subject matter of claims 53 and 62 are *prima facie* obvious. Applicants respectfully request withdrawal of the rejection.

### **CONCLUSION**

Applicants believe that the foregoing constitutes a complete and full response to the Office Action of record. Accordingly, an early and favorable action on the merits is respectfully requested. If a telephone conversation would further the prosecution of this case, the examiner is invited to telephone the undersigned at his convenience.

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